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“frontiers of science”

*In Vivo Magnetic Resonance*

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**Chair, Charles S. Springer  
Vice-Chair, Richard B. Buxton**

# **Onward and Downward:**

## **Higher MRI Field Strength Means Lower Detection Thresholds**

### **for Contrast Reagents**

**{"Seeing Less with More," W. D. Rooney}**

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# **Non-Diamagnetic Contrast Reagents (CRs) for MRI**

## **I. Monomeric**

(paramagnetic, mononuclear Gd(III), Mn(II) chelates, complexes)

- used to catalyze  $^1\text{H}_2\text{O}$   $\text{R}_1$  [ $\equiv (\text{T}_1)^{-1}$ ] and  $\text{R}_2$  [ $\equiv (\text{T}_2)^{-1}$ ]

## **II. Polymeric**

(paramagnetic, polynuclear Gd(III) compounds, aggregates; superparamagnetic iron oxide nanoparticles)

- used mostly to catalyze  $^1\text{H}_2\text{O}$   $\text{R}_2$  [ $\equiv (\text{T}_2)^{-1}$ ]

# **Diamagnetic Contrast Reagents (CRs) for MRI**

(diamagnetic, weakly paramagnetic aqueous solutes)

- used for MT contrast with  $^1\text{H}_2\text{O}$

# “Molecular” Imaging / in MRI, “Targeted” CRs

<u>Target Locus</u>	<u>CR Distrib.</u>	<u>Target</u>	<u>Approach</u>	<u>Ref.</u>
intravascular	vascular	serum albumin; angiogenesis, arthritis/inflammation, atherosclerosis sites	IV CR injection	1
interstitial, cytolemmal outer surface	extravascular	transferrin receptor	implant tumor cells bearing receptor engineered for unregulation/ tumor growth / IV CR injection	2
cytosolic, organellar “cell” imaging (J. A. Frank)	intracellular	cytosolic enzyme	direct CR injection into <i>oocyte</i> / growth & development	3
		endosome	employ natural transporter	
		cytosol	incubate CR with <i>stem cell</i> glial progenitors / ventricular cell injection / tract migration	4
			incubate CR with <i>T cells</i> / IV cell injection / migration to spleen	5

1.Lauffer, et al *Rad.* **207**:529(1998). 2.Weissleder, et al *Nat.Med.* **6**:351(2000). 3.Louie, et al *Nat.Biotech.* **18**:321(2000).

4.Bulte, et al *Nat.Biotech.* **19**:1141 (2001). 5.Dodd, et al *J. Immun. Met.* **256**:89(2001).

# Targeted MRI CRs

## Fundamental Problem

Detection threshold for monomeric Gd chelates at clinical field strengths  
[ex., ~30  $\mu$ M at 2 T (Wedeking, Shulka, Kouch, Nunn, Tweedle, 1999)]

Concentrations of interesting targets [ex., neuroreceptors]  
[ 1  $\mu$ M to 0.1 nM (Nunn, Linder, Tweedle, 1997)]

# Approaches to the Targeted MRI CR Sensitivity Problem

## A. Use of polymeric CRs (lower detection threshold [CR])

- requires macromolecular CR size

## B. Target-catalyzed CR polymerization (aggregation)

- MR amplification (Mramp)

Bogdanov, *et al*, *Mol.Imag.* 1:1 (2002).

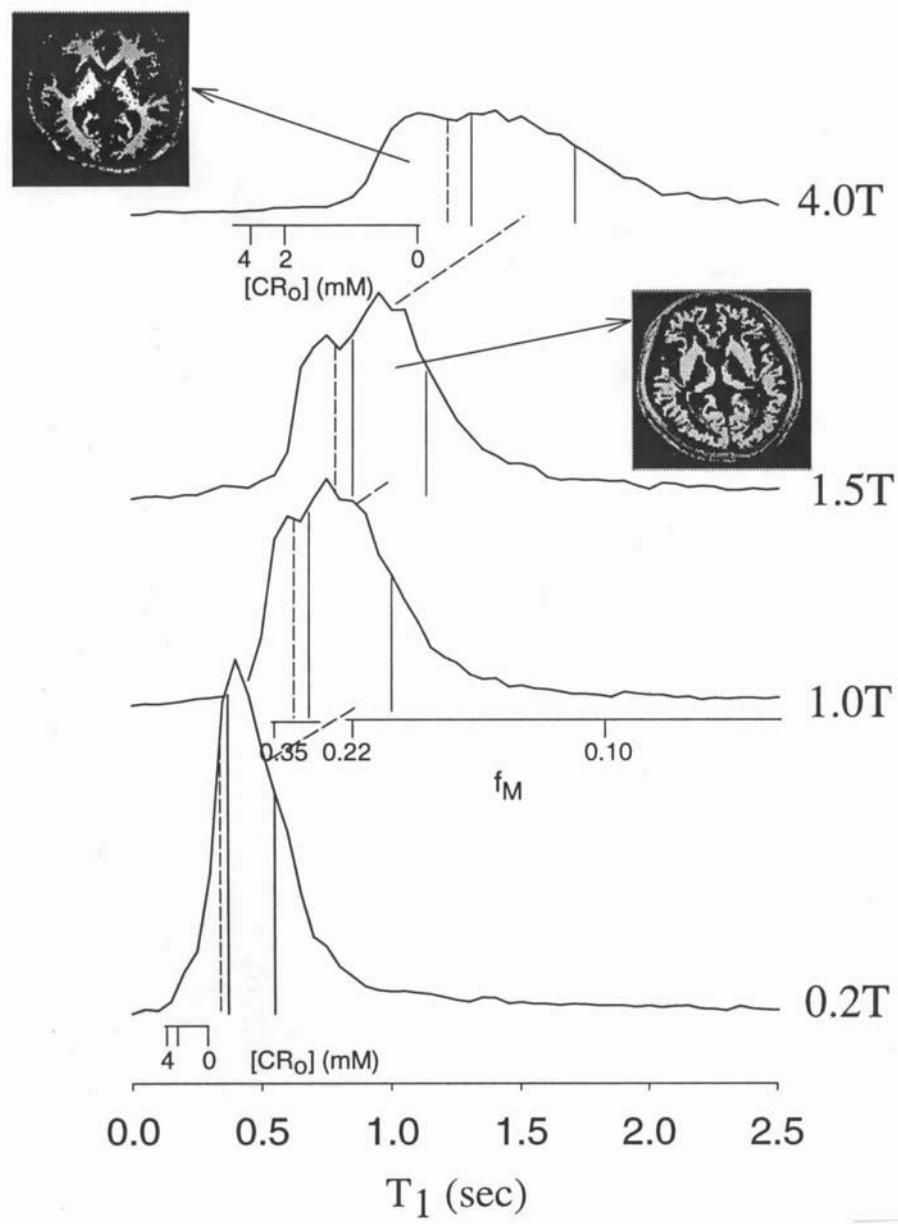
## C. Increased CR relaxivity / reduced molecular rotation / specific binding to natural macromolecule

- receptor-induced relaxation enhancement (RIME)

Lauffer, *et al*, *Rad.* 207:529 (1998).

## D. Use of higher magnetic field

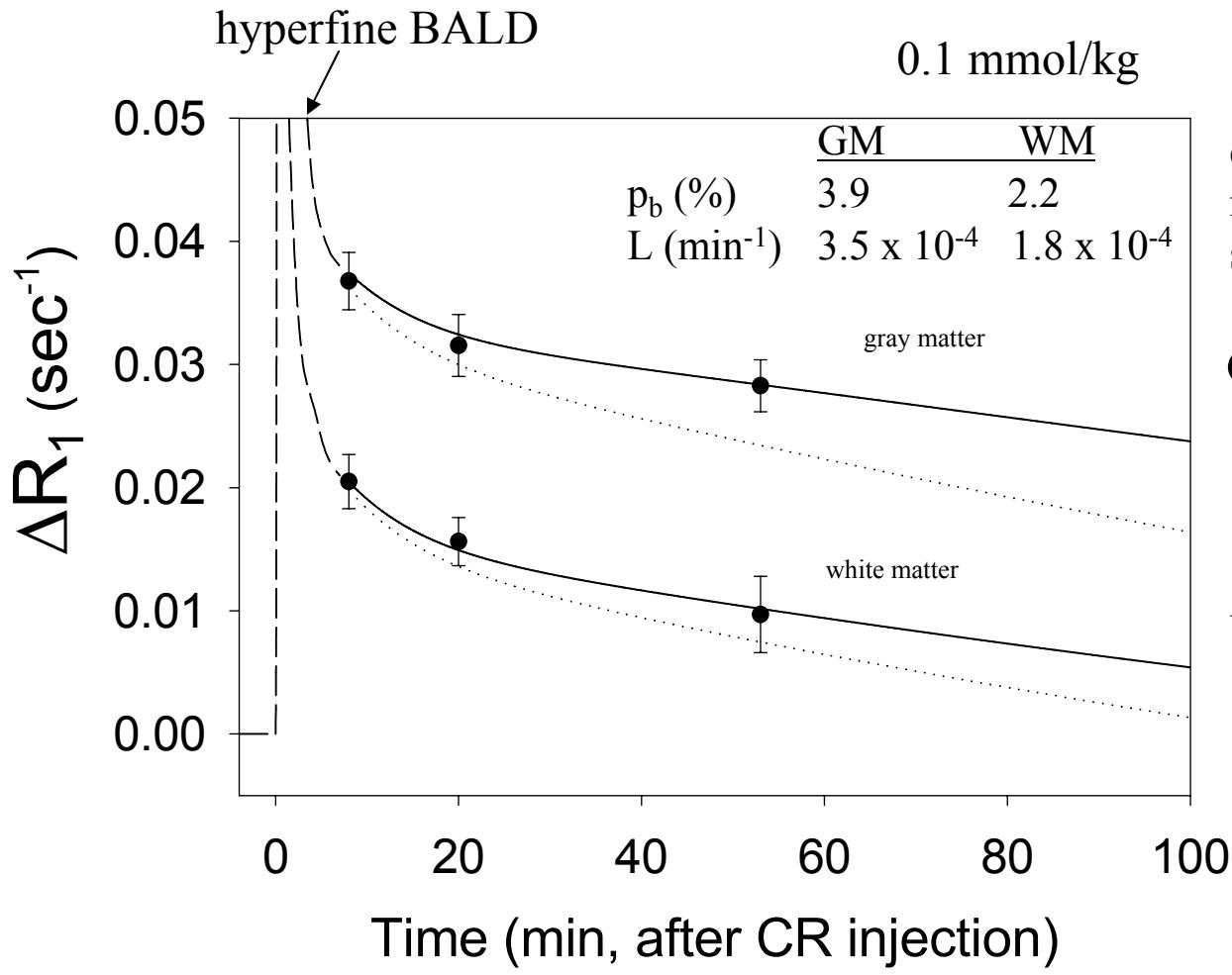
Springer and Rooney, *PISM RM* 9:2241 (2001).

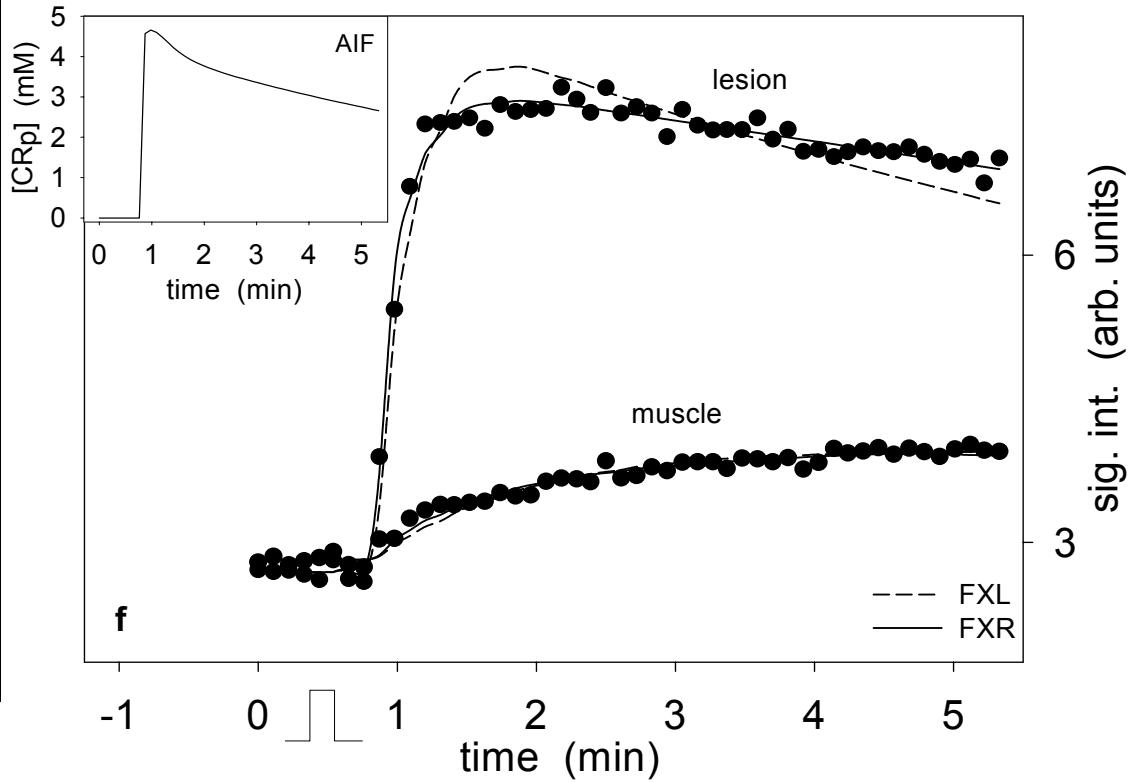


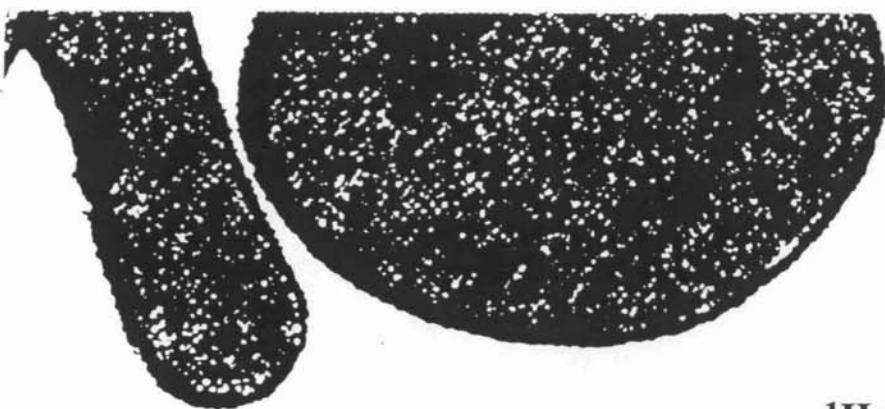
**Rooney**

# Tissue $^1\text{H}_2\text{O}$ $\Delta R_1$ After CR Injection

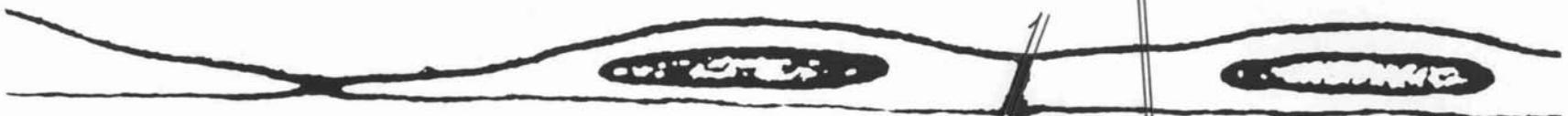
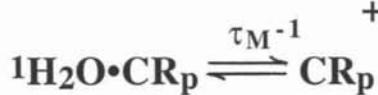
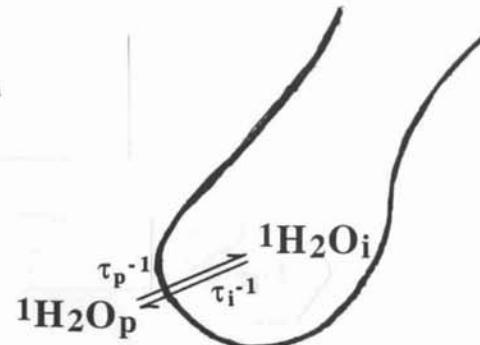
Healthy controls (11M,  $37 \pm 8$  y) / 4 T





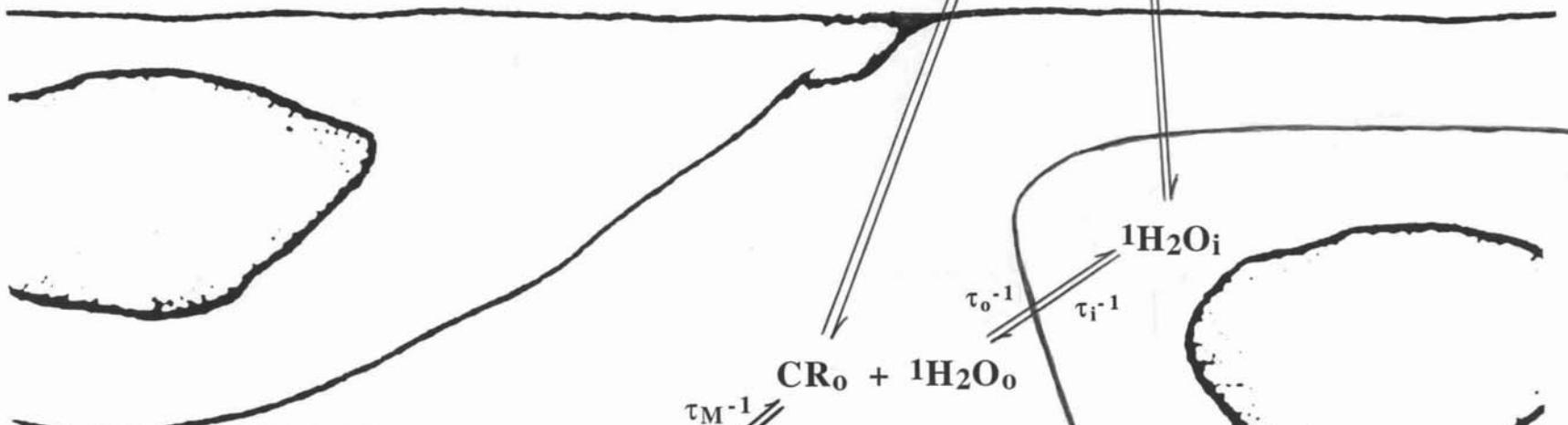


plasma

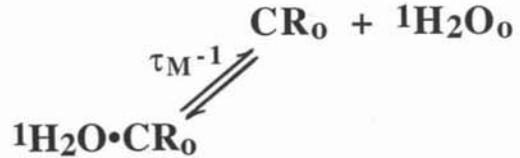


vessel wall

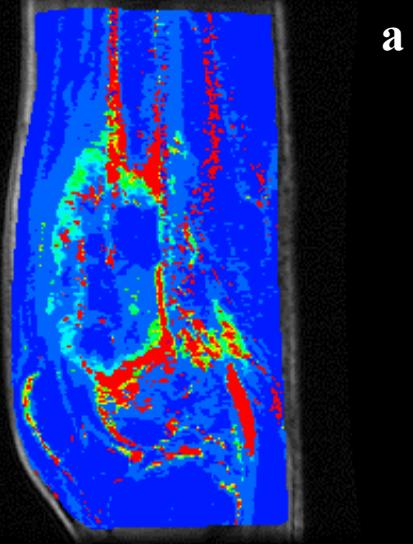
$$\frac{(P_o S \rho / V_o)}{(P_i S \rho / V_p)} \sim \frac{k_{op}}{k_{po}}$$



interstitium

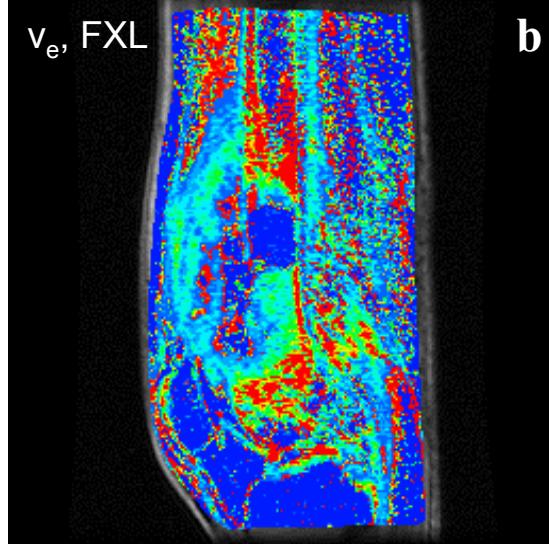


$K_{trans}$ ,  
FXL



**a**

$v_e$ , FXL



**b**

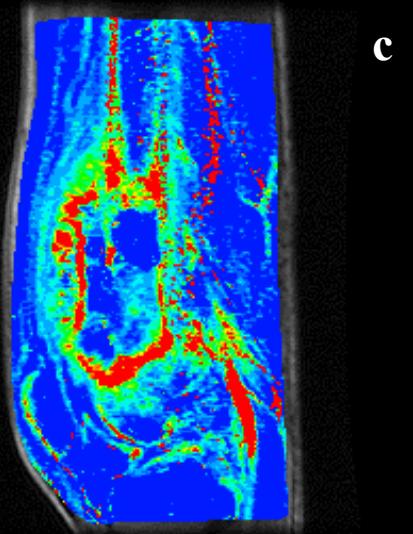
$K_{trans}(\text{min})^{-1}$

0.81  
0.68  
0.55  
0.42  
0.29  
0.16  
0.03

$v_e$   $t_i$  (s)

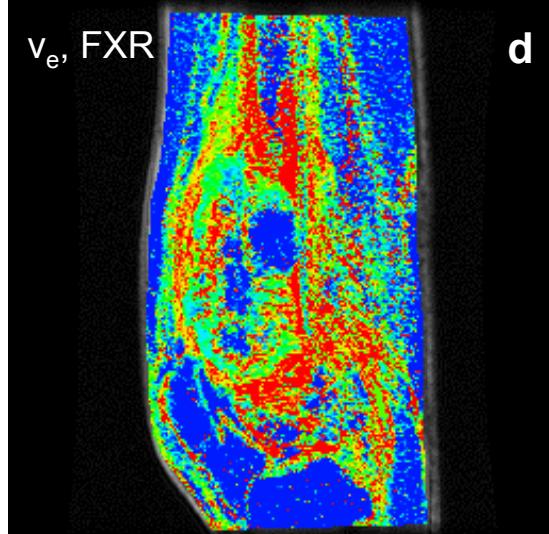
0.65 1.5  
0.55 1.3  
0.45 1.1  
0.35 0.9  
0.25 0.7  
0.15 0.5  
0.05 0.3

$K_{trans}$ ,  
FXR



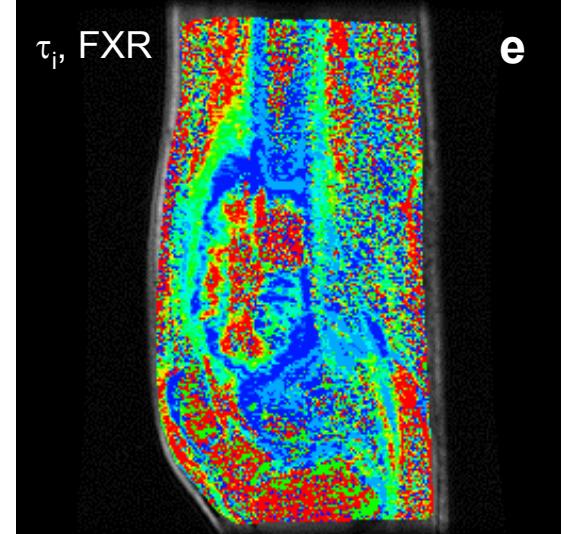
**c**

$v_e$ , FXR



**d**

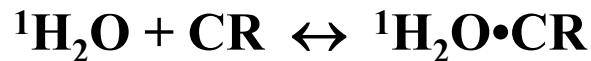
$\tau_i$ , FXR



**e**

**Yankeelov, Rooney, Dyke, Koutcher**

# Conclusions:



$$\mathbf{R}_1 = \mathbf{r}_1[\text{CR}] + \mathbf{R}_{10}$$

$$(\mathbf{R}_i \equiv \mathbf{T}_i^{-1})$$

$$\mathbf{R}_2 = \mathbf{r}_2[\text{CR}] + \mathbf{R}_{20}$$

$$(\mathbf{R}_1 - \mathbf{R}_{10})/\mathbf{R}_{10} = (\mathbf{r}_1/\mathbf{R}_{10})[\text{CR}]$$

$$\mathbf{r}_1 = \mathbf{r}_{1h}$$

$$\mathbf{r}_{1h} = \mathbf{r}_{1I}^{ss} + \mathbf{r}_{1I}^{sC} + \mathbf{r}_{1I}^{dS} + \mathbf{r}_{1I}^{dC} + \mathbf{r}_{1O}^{dS} + \mathbf{r}_{1O}^{dC}$$

h - hyperfine

I - inner sphere

s - scalar

S - Solomon-Bloembergen-Morgan [Gd(III)]

$$\mathbf{r}_{2h} = \mathbf{r}_{2I}^{ss} + \mathbf{r}_{2I}^{sC} + \mathbf{r}_{2I}^{dS} + \mathbf{r}_{2I}^{dC} + \mathbf{r}_{2O}^{dS} + \mathbf{r}_{2O}^{dC}$$

$\chi$  - bulk magnetic susceptibility

O - outer sphere

d - dipolar

C - Curie-Spin [Dy(III)]

Rooney, Medina

# Recommendation:

- support for purchase of high-field instrumentation